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A novel means to classify response to resuscitation in the severely burned: Derivation of the KMAC value☆,☆☆

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ABSTRACT

Background: Resuscitation fluid rates following burn are currently guided by a weight and burn size formulae, then titrated to urine output. Traditionally, 24 h resuscitation is reported as volume of resuscitation received without direct consideration for the physiologic response. We propose an input-to-output ratio to describe the course of burn resuscitation and predict eventual outcomes.

Methods: We reviewed admissions to a burn center from January 2003 through August 2006. Inclusion criteria were ≥20%TBSA, admission ≤8 h after burn, and survived ≥24 h. Demographics, input volume and urine output, and clinical outcomes were recorded. A ratio of input volume (cc/kg/%TBSA/h) to urine output (cc/kg/h) was calculated at 24 h. The ratio of fluid intake to urine output reflecting an 'expected' response was developed: 4 cc/kg/%TBSA/24 h (0.166 cc/kg/%TBSA/h) divided by 0.5–1.0 cc urine/kg/h for an expected range 0.166–0.334. Subjects were classified based upon the ratio: over-responders (<0.166), expected (0.166–0.334), or under-responders (>0.334). Clinical outcomes were compared and concordance of classification to values was calculated at 12 h.

Results: 102 subjects met inclusion criteria; 29 in the over-responders, 37 in the expected, and 36 in the under-responders. Resuscitation volume was directly proportional to the calculated ratio while urine output was inversely proportional. Group mortality was 21%, 11%, and 44%, respectively, with a significant difference between the expected and under-responders ($p < 0.002$). We found decreased ventilator-free days in the under-responders, and when deaths were excluded, decreased ICU-free days as well ($p < 0.05$). Concordance of paired data gathered at 12 h and 24 h was 67% for the under-responder group.

Conclusions: We describe a novel ratio to classify acute resuscitation after severe burn including the patient's response. Such a classification is associated with eventual outcomes.

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1. Introduction

Initial management of severely burned patients focuses on resuscitation with crystalloid solution to restore intravascular volume. Weight and percent total body surface area burn (%TBSA) are used in various formulae to determine the initial intravenous fluid rate [1] and standardized changes in volume infusion. The rate is then commonly titrated hourly to maintain a targeted rate of urine output as an indirect measure of cardiac output, based upon volume per hour, or volume/h per body weight. The formula most commonly used today is the Parkland formula [2] described by Baxter in 1968. The original study stated that the majority of severely burned patients use between 3.7 and 4.3 cc of lactated Ringers'/kg/%TBSA to be adequately resuscitated. Since that time, numerous studies have shown that the majority of patients actually receive more than recommended by the Parkland formula [3–7].

We observed that patients respond differently during resuscitation even when following guidelines, and these differential responses seem to correlate with patient outcome. For example, patients that receive close to the predicted resuscitation volume and maintain an adequate urine output generally do well. However, those who receive large volumes of fluid above the recommended formulae but remain oliguric have poor outcomes. We sought to find a method to use during resuscitation to quantitatively differentiate these populations. This culminated in a novel calculation using crystalloid input and urine output volume to classify patients into outcome groups that reflect not only the volume given, but also the physiologic responses to the resuscitation volume received (Kelly–McLaughlin value, i.e. KMAC).

2. Methods

2.1. Subjects

After Institutional Review Board approval of the protocol, we reviewed all burn unit admissions at our institution from January 1, 2003 to August 31, 2006. Criteria used to admit burned patients into the burn intensive care unit were $\geq$20% TBSA, inhalation injury, circumferential burns, high voltage electrical burn injury or as clinically indicated based on the assessment of the provider. The inclusion criteria for this study were burned patients weighing $\geq$40 kg admitted within 8 h of injury, $>$20% TBSA burned, and survived over 24 h. We excluded prisoners, patients admitted to non-ICU beds, electrical injuries, those with other significant traumatic injuries, and those with incomplete pre-hospital data. Inhalation injury was defined as a history of burn in an enclosed space and evidence of upper airway injury on bronchoscopy. Burn size and depth were determined by the attending surgeon within 48 h of injury. Weight was determined at admission.

Resuscitation was initiated with lactated Ringers' solution using the Modified Brooke Equation (2 cc/kg/%TBSA) or the Parkland formula (4 cc/kg/% TBSA), and titrated to a urine output of 30–50 cc/h without particular protocol. Albumin use was at the discretion of the provider. All intravenous fluid (crystalloid, colloid, blood products), oral intake (by mouth, nasogastric, or feeding tubes), and urine output was totaled during the first 24 h, including pre-hospital volumes. Blood product volumes were estimated based upon mean blood bank values; 1 unit of packed red blood cells (PRBC) = 350 ml, and 1 unit of fresh frozen plasma (FFP) = 250 ml; no other blood products were administered. Outcomes evaluated were in-hospital mortality, abdominal compartment syndrome (ACS), extremity compartment syndrome (ECS), hospital days, ventilator days, and ICU days. Abdominal compartment syndrome was determined by those who underwent laparotomy within 48 h of admission in conjunction with measured intra-abdominal pressures over 30 mm Hg.

2.2. Ratio calculation

The ratio was calculated by dividing the 24 h total resuscitation volume (cc/kg/%TBSA) by 24 to establish a mean per hour volume (cc/kg/%TBSA/h). This was then divided by the 24 h urine output (cc/kg/h) to give a unitless number. An example of the calculation is shown (Fig. 1). Standard norms were used to establish reference ranges; 4 cc/kg/%TBSA//24 h becomes 0.166 cc/kg/%TBSA/h for the input volume, and 0.5–1.0 cc/kg/h as a targeted normative urine output volume commonly used during resuscitation, giving an expected range 0.166–0.334.

The ratio was calculated at 24 h with assignment of subjects into groups above, within, and below the normative range established above. Comparisons were then made between groups. Then, values for the same subjects calculated at 12 h were paired with correlations and concordance calculated.

2.3. Statistical analysis

ANOVA with Tukey's test for multiple comparisons or Student's *t*-test was used to analyze continuous variables. Kruskal–Wallis analysis by ranks was used where appropriate. Dichotomous variables were compared using χ^2 or Fisher's exact test. Regressions were linear and polynomial (3 degrees). Statistical significance was set at $p < 0.05$. Values are reported as mean $\pm$ SEM unless otherwise indicated.

$$\frac{\text{4 cc/kg/\%TBSA burned (desired resuscitation volume)}}{\text{24 hours}} = \text{0.167cc/kg/\%TBSA per hour}$$

$$\frac{\text{0.167 cc/kg/\%TBSA per hour}}{\text{0.5-1.0 cc/kg/hour}} = \text{0.167 to 0.333}$$

Fig. 1 – Derivation of KMAC values based on optimal resuscitation volume[2] divided by optimal urine output.

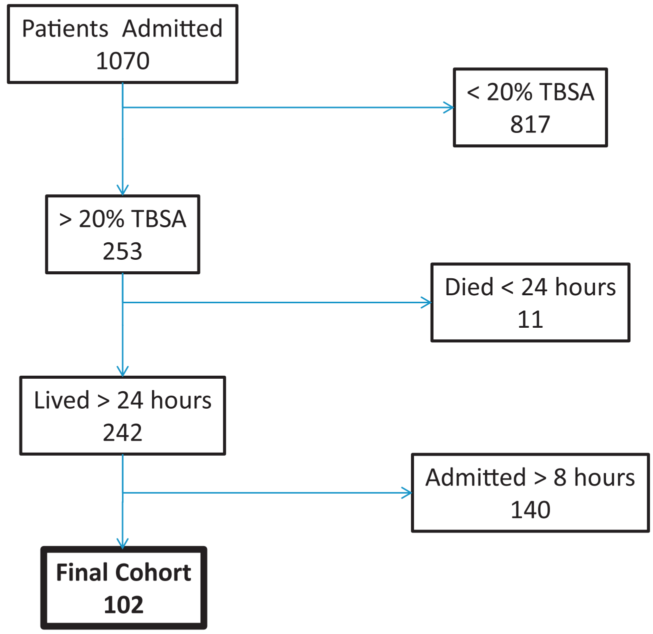

Fig. 2 – CONSORT diagram for subject enrollment.

3. Results

One-hundred two subjects, 73 men and 29 women, with ages of 42 years ± 1.8 met inclusion criteria for the study (Fig. 2). Demographic data are shown in Table 1. The 24 h resuscitation volume was 5.5 ± 0.3 cc/kg/%TBSA that approximated a normal distribution with skew to the left (Fig. 3a), urine output was an average of 74 ± 4 cc/h or 0.9 ± 0.1 cc/kg/h (Fig. 3b) with a similar skew to the left. The predicted resuscitation volume, based on the Parkland formula, was 13.6 ± 0.7 L, while the actual volume was 18.4 ± 1.25 L ($p < 0.001$).

3.1. *Ratio groups*

After calculation of the ratio at 24 h, subjects were assigned post hoc to respective groups: over-responders (<0.167), expected (0.167–0.333), and under-responders (>0.333). Subjects with low ratio values (<0.167) had higher urine outputs than targeted relative to fluid infused (over-responsive), expected subjects had the targeted response of 0.5–1.0 cc/kg/h, and subjects with high ratio values (>0.333) had lower urine outputs than targeted in relation to relatively higher

Table 1 – Demographics of the study population.

Gender (% men)	72
Age (years)	42 ± 1.8
% TBSA	40 ± 2
% FT	17 ± 2
Inhalation injury (%)	28
In-hospital mortality (%)	25
24 h resuscitation (cc/kg/%TBSA)	5.5 ± 0.3
24 h urine output (cc/h)	73.5 ± 3.9
24 h urine output (cc/kg/h)	0.89 ± 0.05

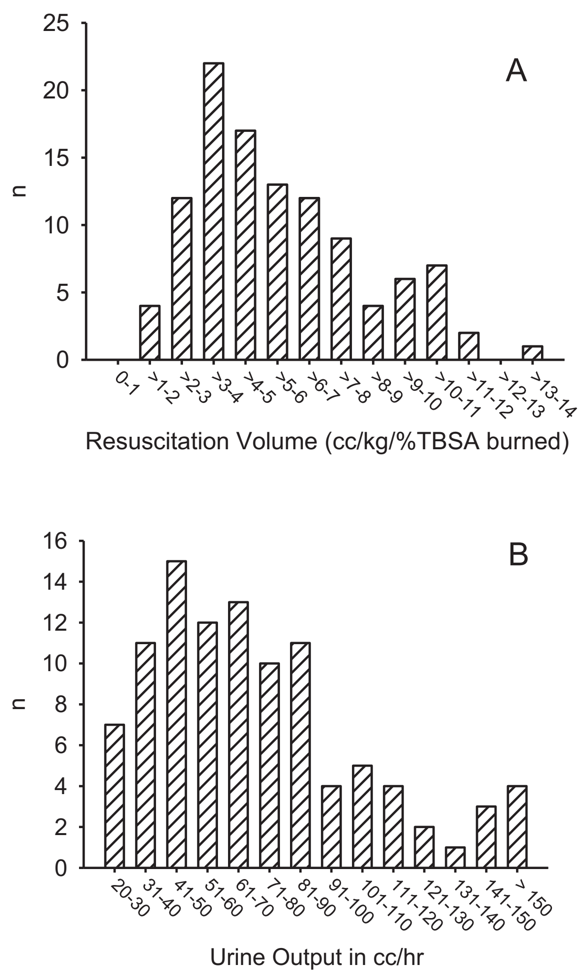

Fig. 3 – (A) Frequency distribution for 24 h resuscitation volume (cc/kg/%TBSA); the Parkland formula recommends 4 cc/kg/%TBSA. (B) Urine output in cc/h for this adult population; target range was 30–50 cc.

Table 2 – Demographic data for the three groups defined after ratio calculation. Comparisons for low and high groups were to the desired group.

	Low ($n = 29$)	Expected ($n = 37$)	High ($n = 36$)
Gender (% men)	83%	73%	61%
Age (years)	40 ± 3.1	38 ± 2.6	49 ± 4 *($p = 0.02$)
%TBSA	38 ± 3.2	39 ± 2.9	43 ± 3.2
%FT	14 ± 4.2	13 ± 2.9	24 ± 4 *($p = 0.03$)
Inhalation injury (%)	10%	24%	47% ($p = 0.052$)
24 h resuscitation (cc/kg/%TBSA)	3.5 ± 0.27 *($p < 0.001$)	5.3 ± 0.38	7.4 ± 0.4 *($p < 0.001$)
24 h urine output (cc/h)	106 ± 7 *($p < 0.002$)	76 ± 6	45 ± 3 *($p < 0.001$)
24 h urine output (cc/kg/h)	1.24 ± 0.097 *($p = 0.02$)	0.94 ± 0.076	0.5 ± 0.04 *($p < 0.001$)

volumes, and thus were relatively resistant to resuscitation (under-responsive). After this assignment, 29 subjects were in the over-responder group, 37 in the expected, and 36 in the under-responder group. Demographic data for each group are shown in Table 2. Those in the under-responder group were older with greater full-thickness burns ($p < 0.05$). The difference in burn size, however, is accounted for by the formulae in the analyses.

3.2. *Over-responders (<0.166)*

These subjects had significantly lower resuscitation volumes indexed to urine output than the normal group (3.5 cc/kg/%TBSA $\pm$ 0.27 vs 5.3 cc/kg/TBSA $\pm$ 0.38, $p < 0.001$), and a significantly higher overall urine output (1.24 cc/kg/h $\pm$ 0.097 vs 0.94 cc/kg/h $\pm$ 0.076, $p < 0.02$). For these reasons, we propose to call this group the 'over-responders' as urine output was higher than targeted. They also received significantly less fluid than the other groups. No significant differences were found in all clinical outcomes between this group and those of the normal group. Outcome data for the groups are shown in Table 3.

3.3. *Expected (0.166–0.334)*

These subjects fell within the reference range set by modeling 4 cc/kg/%TBSA and 0.5–1.0 cc/kg/h for urine output. For this reason we propose these as 'expected responders'. All comparisons are made to this group as the normal response, and therefore serve as controls.

3.4. *Under-responders (>0.334)*

This group had significantly higher resuscitation volumes compared to the normal group, 7.4 ± 0.4 cc/kg/%TBSA vs 5.3 ± 0.4 cc/kg/%TBSA ($p < 0.001$), and a significantly lower urine output, 0.60 ± 0.04 cc/kg/h vs 0.90 ± 0.08 cc/kg/h ($p < 0.001$), but still within the 0.5–1.0 cc/kg/h range. Thus, we propose these as the 'under-responders'. The percentage of subjects in this group with inhalation injury was higher than in the expected group, 47% vs 24% which just achieved statistical significance ($p = 0.05$). Mortality rate was 4 times that of the desired group, 44% vs 11% ($p = 0.002$).

3.5. *Performance*

Overall, we found no difference in hospital days, ICU-free days, or abdominal compartment syndrome rates between the three groups (Table 3). However, we did find the under-responder group had a decrease in ventilator-free days, indicating that more ventilator time and resources were used for this group compared to the expected group. When deaths were excluded from all groups, we found that ICU-free days were significantly lower in the under-responder group compared to the expected group and over-responder group (over-responders 20 ± 2 days, expected 17 ± 2 days, and under-responders 10 ± 2 days*) (*$p < 0.05$), indicating that increased ICU time was also present in the under-responders. Ventilator-free days were also lower in the under-responders compared to the other groups (25 ± 1 low, 22 ± 1 desired, and 15 ± 2 high*) (*$p < 0.05$).

3.6. *Qualification*

We then performed an analysis whereby the ratio was calculated at 12 h for the same subjects and compared to the 24 h value in an effort to show whether the 12 h value predicted the 24 h results. A linear regression revealed an adjusted r^2 of 0.47 indicating modest correlation. In examining the data closely, most of the variance appears in those starting in the under-responder range (Fig. 4a). To address this observation, we spread the 12 and 24 h data by ranks from 1 (low) to 102 (high) and repeated the regression. We found that variance is distributed across the range for rank, but the r^2

Table 3 – Outcome data for the three groups defined after ratio calculation. Comparisons for the low and high groups were to the desired group (ACS, abdominal compartment syndrome). ICU and vent free days are within the first 28 days.

	Low ($n = 29$)	Expected ($n = 37$)	High ($n = 36$)
Hospital days	31 ± 8	43 ± 8	44 ± 9
ICU free days	18 ± 2	19 ± 3	13 ± 2
Ventilator free days	22 ± 2	19 ± 3	17 ± 1 *($p < 0.05$)
ACS (%)	0	5 ($n = 2$)	14 ($n = 5$) ($p = 0.26$)
Mortality (%)	21	11	44 *($p = 0.002$)

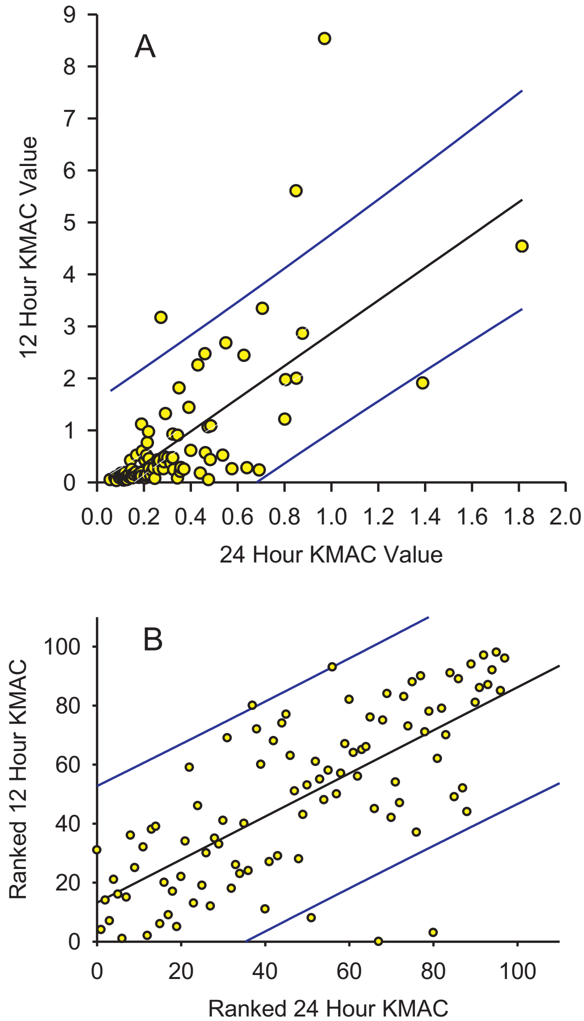

Fig. 4 – Regressions of 12–24 h KMAC values. The first (A) is a linear regression of paired 12 and 24 h data. Variability increases with increasing 24 h KMAC values ($r^2 = 0.48$). To further demonstrate potential effects at low 24 h KMAC values, the values were ranked from 1 to 102 and paired (B). In this analysis, variability seems to be distributed across the range, but with higher correlation ($r^2 = 0.57$). The middle line is the line of regression, and the outside lines are prediction intervals.

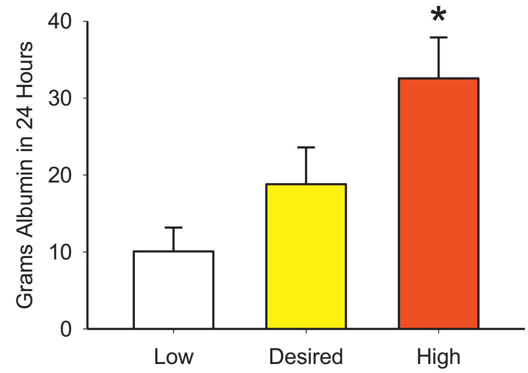

Fig. 5 – Volume of albumin given in the three groups in the first 24 h after injury. The group with high KMAC values received the most albumin (*$p < 0.05$).

value improved to 0.57 (Fig. 4b). In particular, if those above a rank of 66 for the 24 h value are considered, i.e. those in the under-responder group, 24 of 36 were above the line of regression at 12 h. Therefore, a high 12 h value (>0.334) gives a reasonable estimate (67%) of those in the under-responder group at 24 h. Of note, we found no correlation of 24 h KMAC value to burn size, indicating no independent association to injury severity.

To further define the relationship of values at 12 and 24 h, we compared the concordance of values by groups. If the subjects are grouped at 12 h into the defined ranges, the concordance is 67% for the over-responders staying in the assigned group at 24 h (22 [24 h value]/33 [12 h value] correct), 42% for the expected group (9/21 correct), and 56% for the under-responders (27/48 correct). In general, those at the extremes of the low and high range at 12 h stayed within the group at 24 h.

Our final analysis was to determine whether differences could be found between groups on the use of colloids during resuscitation and whether this had any effect on our new ratio. When infused colloid volume in grams was examined, we found that albumin use and volume was actually highest in the high group (Fig. 5) perhaps reflective of the provider use of albumin to treat lack of response to crystalloid during the resuscitation in this uncontrolled study.

4. Discussion

Since the initial reports of the burn resuscitation formulae [2,3], numerous studies demonstrated that the majority of severely burned patients receive more than the predicted 4 cc/kg/%TBSA resuscitation in the first 24 h [4–7]. Many of these describe qualitative differences in outcomes with high infusion volumes, however, ideal resuscitation volume and how to classify adequacy of resuscitation quantitatively in relation to response remain undetermined. In this study, we describe a novel means by which to classify the response to acute resuscitation in the severely burned which we term the KMAC value. By using resuscitation volume *indexed* to urine output, we defined three distinct groups of subjects with differing response to resuscitation; over-responders, normal-responders, and under-responders. As expected, the under-responders received more resuscitation volume, have a diminished response to such volume, and have poorer outcomes. We found utility in making this determination in that values determined at 24 h assigning persons to the under-responder group associated with poorer outcomes correlate to paired values at 12 h 67% of the time. Therefore, at 12 h, relatively unsuccessful resuscitative efforts can be identified with relative confidence for those with poorer outcomes, and might indicate futility of increased intravenous volumes and rather direct toward other resuscitation adjuncts such as colloid use or hemofiltration/plasma exchange. These treatments should be tested in this population.

The importance of appropriate resuscitation volume cannot be overstated. Previous work showed that complications increase with under [7] and over-resuscitation [8–11]. Unfortunately, the classification of over or under-resuscitation is sometimes not known until complications occur. Although burn resuscitation formulae recommending fluid volume infused have stood the test of time in relation to decreasing renal failure associated with acute burns [12], it is apparent that the response to injury, in this case urine output, for every patient and burn size is unique Thus, a different but appropriate resuscitation volume exists for each patient. Our conclusions are based upon the premise that providers are striving to maintain urine output while minimizing fluid given. This is done with greater skill by some, while others are not done as well. The ratio which we define in this paper can be used as a tool during resuscitation to determine appropriate volumes more accurately, but must be anchored by the relative volume being given with continued efforts to decrease fluids appropriately and minimize morbidity associated with over-resuscitation (i.e. resuscitation morbidity). For instance, 5.0 cc/kg/%TBSA is higher than predicted by the Parkland formula, but below our mean resuscitation volume of 5.5 cc/kg/%TBSA. Whether this patient was under, ideally, or over-resuscitated cannot be determined by assessment of intravenous volume infused alone. Patient response of not only urine output, but also other indicators of physiologic equilibrium are the ultimate testimony to the efficacy of resuscitation efforts. The addition of urine output into a ratio at least partially takes this into account.

In deriving the formula, it should be noted that the input value in cc/kg is divided by the output value in cc/kg. For the purposes of resuscitation volumes, weight can be considered as constant, thus in calculating the KMAC value for an individual, weight can be omitted. Thus, the formula can also be calculated as follows: [volume in (cc)/urine out (cc)]/[% TBSA burned $\times$ 100].

One potential benefit of using this method to assess resuscitation is that it can be determined before 24 h to quantitate the eventual response. When the 24 h value was compared to a ratio collected at 12 h, we found that concordance for the low and normal groups was relatively strong, and those in the high group had the most variation for assignment later in the course. Perhaps this occurred because of routine revisions of fluid delivery upwards in response to oliguria more common early in resuscitation which resolves in some, thus, a higher KMAC value might be expected in part of the population that will eventuate in the normal range. In addition, perhaps over-resuscitation was detected by the providers with appropriate adjustments in this non-controlled study to describe some of this divergence. Secondly, perhaps internal feedback from increased fluids induced endogenous shifts that led to functional improvement. Non-linear modeling of the response and thus the KMAC over time might shed more light on this possibility, but is outside the scope of this study. Regardless, a high ratio at 12 h clearly indicates increased risk for large volume resuscitation and increased mortality and increased ventilator days and ICU days in survivors. From a clinical perspective, the ratio could be collected at 12 h to indicate those likely to continue to be difficult to resuscitate, and adjuncts might be considered such as colloid solutions, anti-inflammatory agents, vasoactive medications, or plasmapheresis/continuous renal replacement therapies without volume removal [13].

Mortality rate was increased in the high KMAC group. However, these under-responders were older and had greater percent of full thickness burns, and both increasing age and burn size are traditional markers of burn mortality. While burn size is accounted for in the ratio which is included in the calculations, age is not. Nonetheless, the tool identifies those with all ages and burn sizes who are not responding as hoped or expected. This patient group may benefit from adjuncts to traditional resuscitation earlier in the course to avoid high volumes of crystalloid and resuscitation morbidity.

Interestingly, we found that albumin use as a colloid was actually highest in the high ratio group intimating that this therapy may not have been as effective as hoped in decreasing total volumes infused and the subsequent urine output response. The practice at our unit has been to use albumin as an adjunct to resuscitation in those receiving high volumes of crystalloid and thus albumin use in this group was likely biased in this non-controlled study. However, it must be noted that 44% ($n = 21$) of those with a high value at 12 h eventuated in the normal group. Of the 48 with high KMAC values at 12 h, all received albumin during the resuscitation after 12 h. It could be speculated that albumin treatment contributed to decreasing volumes infused, but this would require a study where some did not receive albumin as controls.

Of interest, the under-responders also consumed more ICU time and ventilator time. These findings are then associated with higher volumes received with lower relative urine outputs. It is possible that the method or mode of ventilation (e.g. being on a mechanical ventilator) led directly to changes in fluid responsiveness. This should be examined in more detail with directed comparison between matched patients with and without mechanical ventilation. Recent evidence suggests that burned patients are more commonly subjected to mechanical ventilation, sometimes unnecessarily [14], which may in part explain higher resuscitation volumes seen in the current era.

The proposed ratio uses urine output as the marker for resuscitation adequacy. While this is certainly the traditional method of assessing resuscitation adequacy, other measures such as blood pressure, peripheral perfusion, and cardiac output when available should also be considered by the provider as output measurements during the course of treatment. The ratio, then, should be used as another tool in the armamentarium to determine proper treatment. In particular, those with severe inhalation injury may have significant alterations in fluid physiology due to lung changes in addition to peripheral changes; this should certainly be kept in mind during the course of resuscitation. Ultimate utilization of this ratio to determine treatments that might improve outcomes must be addressed in later studies.

In conclusion, we describe a novel calculation which can be used during resuscitation in the severely burned patients to classify their response. Its use identifies three unique groups among severely burned patients. One specific group of

patients, the under-responders who had high KMAC values, are older, have a greater percent of full-thickness burns, and an increased mortality rate. They might benefit from adjunctive therapies to the traditional crystalloid resuscitation. Further investigation as to the clinical utility of using the KMAC ratio is warranted [15].

Conflict of interest statement

None.

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